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The Serpentine Sign: A Reliable Endoscopic and Radiographic Finding in Empty Nose Syndrome

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Objective: Empty nose syndrome (ENS) is a relatively uncommon disease that greatly impacts the quality of life and presents diagnostic challenges. We sought to identify objective clinical findings unique to patients with ENS, and in doing so identified compensatory mucosal hypertrophy in an alternating, undulating swelling on endoscopy and coronal computerized tomography (CT) that we have termed the "Serpentine Sign." Here, we investigated whether this radiographic finding is a reliable manifestation in ENS patients.

Methods: Retrospective review was undertaken to identify ENS patients with past turbinoplasty, an ENS6Q score of at least 11/30, and symptomatic improvement with the cotton placement test. Control patients without complaints of ENS symptoms (ENS6Q < 11) were identified for comparison. ENS and control patients had coronal CT imaging available to evaluate for the Serpentine Sign, as well as ENS6Q scores, and histologic analysis of nasal tissue.

Results: 34 ENS and 74 control patients were evaluated for the presence of the Serpentine Sign. Of the 34 patients with ENS, 18 exhibited this radiographic finding on CT imaging (52.9%) compared to 0 of the 74 control patients ($p < 0.0001$). Further analysis demonstrated that ENS patients with the Serpentine Sign had lower median scores on ENS6Q than ENS patients without (17.5 vs. 22, $p = 0.033$). Histology revealed disorganized subepithelium rich in seromucinous glands similar to the nasal septum swell body.

Conclusion: The "Serpentine Sign" is a unique presentation of hypertrophic change to the nasal septum soft tissue that is specific to ENS patients and may serve as a reliable radiographic and endoscopic finding in diagnosis.

Key Words: empty nose syndrome, ENS, mucosal hypertrophy, paradoxical nasal obstruction, suffocation, turbinate reduction, turbinectomy, turbinoplasty, upper airway.

Level of Evidence: IV

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INTRODUCTION

Empty nose syndrome (ENS) is a rare disease entity characterized by paradoxical nasal obstruction and other nasal symptoms.[1] While the exact pathophysiology appears to be multifactorial, ENS is most commonly associated with iatrogenic tissue loss following turbinoplasty procedures. Recent advances in ENS treatment, including surgical augmentation via injection of temporary fillers such as carboxymethylcellulose gel, hyaluronic acid, and placement of permanent implant materials such as cadaveric rib cartilage through inferior meatus augmentation procedures (IMAP), have shown success in reducing symptom burden and increasing quality of life in this patient population.[2–13] However, ENS remains a diagnostic challenge that may prevent or prolong the time to treatment. This is in part due to wide patient variability in patients presenting with a range of symptoms, often suffering from concomitant sinusitis, and showing varying levels of turbinate tissue loss.[14] Additionally, endoscopic and radiographic findings are often subtle and considered nonspecific by many physicians. While the validation of the ENS Questionnaire-6 (ENS6Q) has played an essential role in both diagnosing ENS and monitoring treatment response, as well as the use of the in-office cotton test, an enhanced understanding of objective imaging findings would further aid in accurately identifying this condition and would reduce prolonged time to treatment that patients with ENS often experience.[2,15–18]

Prior studies have shown that patients with ENS often display aberrant intranasal mucosal thickening on radiographic imaging, though this has not yet been further examined in relation to patient symptamotology.[19,20] We, therefore, aim to define, explain, and test the reliability of our group's previously unidentified imaging finding, which we have termed the "Serpentine Sign," (SS) as an objective finding strongly associated with ENS.

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MATERIALS AND METHODS

Following approval from the Stanford University Institutional Review Board, we conducted a retrospective review of ENS patients at the Stanford University Sinus Center. Medical records of ENS patients previously tracked in our ENS research database between 2014 and 2019 were reviewed. A cohort of control patients without ENS symptomatology was also identified using the Stanford Medicine Research Data Repository (STARR) database as well as through other pre-existing cohorts of patients seen at the Stanford Sinus Center without ENS. Approximately half of the control cohort had a history of inferior turbinate reduction (ITR) while the remaining had no history of turbinate surgery. Control patients with a history of ITR were required to have computerized tomography (CT) imaging at least 10 years following turbinate surgery as an effort to fairly compare these patients' scans at a similar postoperative time point to our ENS patients, and to allow for the development of the Serpentine Sign if possible. Patients with a history of head and neck cancer and/or head and neck radiation therapy, nasal polyps affecting septal mucosa, autoimmune disease, a history of nasal septectomy, and/or the presence of septal perforations in our region of interest were excluded from both groups. ENS patients were included if they had an ENS6Q score of at least 11 and experienced an improvement in symptoms during cotton testing. The ENS6Q is a previously validated patient questionnaire evaluating six subdomains including dryness, sense of diminished nasal airflow, suffocation, nose feeling to open, nasal crusting, and nasal burning that is highly specific and sensitive for ENS evaluation and identification.[15] A total of 74 ENS and 470 control charts were reviewed. A total of 34 patients with ENS and 74 patients without ENS met inclusion criteria leading to subsequent analysis of corresponding CT images.

Presence or lack of the Serpentine Sign (SS) was evaluated in the 108 patients that met the inclusion criteria. Each CT scan was evaluated at the level of the central septum, using the anterior ethmoid artery (AEA) as a landmark. To standardize our evaluation, septal mucosa was evaluated within 2 cm (±) of the AEA at the level of the inferior turbinate attachment site or below which was identified as the region most affected by tissue loss in our patients with ENS. Measurements were taken bilaterally from the medial septal bone to the lateral mucosa of the septum using Centricity Enterprise Web™ software (GE Medical Systems Informational Technologies, Waukesha, WI). For patients with at least 2 consecutive curvatures along this specific area, measurements were taken of the swellings, as well as the distance between the swellings for a total of three measurements per side (Fig. 1A). For patients who did not appear to have any swellings (i.e., had a fairly consistent thickness of septal mucosa), measurements were made in the same manner at three evenly spaced regions along the septum (Fig. 1B). A patient was considered positive for the Serpentine Sign if coronal CT imaging demonstrated at least one side of the central septum with two or more swellings that measured at least twice as thick as the mucosa in between, at the level of the IT attachment or below. ENS6Q scores of ENS patients, time between turbinate surgery and CT imaging, and history of septoplasty were also collected. To further characterize this tissue, three ENS patients with the Serpentine Sign and two control patients consented to biopsies of their septal mucosa for histologic analysis.

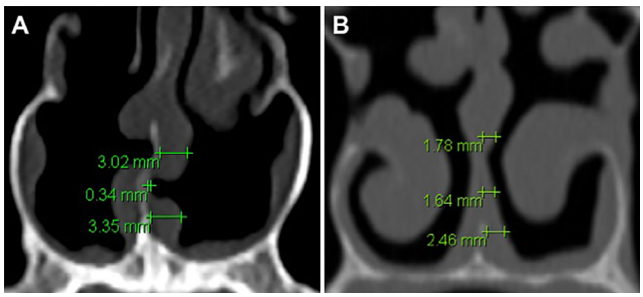

Fig. 1. Measurements on coronal computerized tomography (CT) imaging. (A) Septal mucosa measurements of an Empty nose syndrome (ENS) patient with Serpentine Sign (SS). (B) Septal mucosa measurements of a control patient without SS. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Samples were processed for paraffin embedding, and representative sections were stained with hematoxylin–eosin and picrosirius red for collagen deposition by the Histo-Tek Laboratory (Hayward, CA). Slides were imaged in our laboratory at 4× and 10× magnifications for qualitative analysis and representative images were selected (Fig. 2).

Statistical Analysis

A two-sided Fisher's exact test was used to calculate the statistical significance of the association between ENS and the presence of SS, as well as the relationship between a history of septoplasty and the Serpentine Sign within the ENS patient cohort. A Mann–Whitney U test was performed to (i) determine any statistical significance between the number of years between turbinate surgery and CT imaging and "presence of SS," (ii) to analyze ENS6Q score averages of ENS patients with the Serpentine Sign compared to those without, and (iii) to compare septal mucosa thicknesses in groups without the Serpentine Sign. A Wilcoxon matched-pairs signed rank test was performed to determine if the swellings were significantly thicker than "normal" mucosa in patients positive for the Serpentine Sign. A value of $p < 0.05$ was considered statistically significant for all analyses. Graphpad Prism version 5.0 (GraphPad Software, La Jolla, CA, USA) was used for analysis.

RESULTS

The clinical history and radiographic imaging of 74 patients with ENS and 470 patients without ENS were reviewed. A total of 34 patients with ENS and 74 patients without ENS met the inclusion criteria and were analyzed. In the ENS-positive cohort, 18/34 patients demonstrated the presence of the Serpentine Sign on coronal CT imaging (52.9% of ENS patients) versus 0/74 control patients ($p < 0.0001$). In our ENS positive cohort, median ENS6Q score for ENS patients with the Serpentine Sign was 17.5 (IQR = 14.75–21.75) and without the Serpentine Sign was 22 (IQR = 19.25–25.25, $p = 0.033$) (Table I). Figure 3 depicts representative CT images of patients either positive or negative for the Serpentine Sign.

Further sub-group analysis within the ENS cohort identified a lack of association between the development of the Serpentine Sign and the time following surgery. Analysis of the number of years between a patient's first turbinate surgery/procedure and CT imaging showed that while the number of years was greater in the patients with the Serpentine Sign (median = 14, IQR = 7–23), than those without (median = 8, IQR = 3.3–20), this did not reach statistical significance ($p = 0.195$) (Table I). The majority of patients in both cohorts (ENS-positive and ENS-negative) had a history of septoplasty which

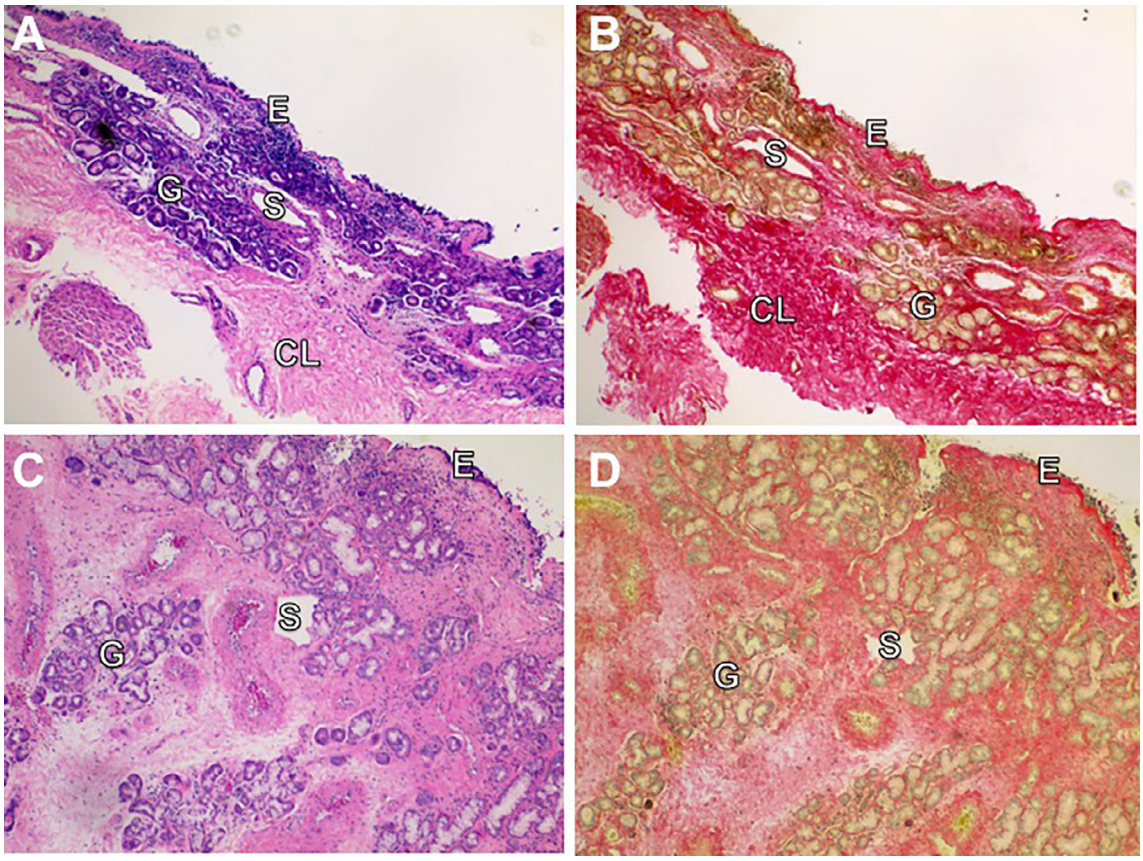

Fig. 2. Histological analysis of septal mucosa from a representative control patient and empty nose syndrome (ENS) patient with the Serpentine Sign. The epithelium (E), sinusoids (S), seromucinous glands (G), and collagen (CL) are labeled within the appropriate images. All images were taken at 10×. (A) Hematoxylin and eosin (H&E) staining of normal septal mucosa from a control patient. (B) Picrosirius red staining of normal septal mucosa from the same control patient demonstrating stratified mucosa with distinct layers of epithelium (E), sinusoids (S) and clusters of seromucinous glands (G), and collagen (CL). (C) Hematoxylin and eosin staining of hypertrophied septal mucosa from an ENS patient with the Serpentine Sign. (D) Picrosirius red staining of hypertrophied septal mucosa from the same ENS patient demonstrating a disorganized subepithelium beneath the epithelial layer (E). A thickened subepithelium with sinusoids (S) and increased clusters of seromucinous glands (G) dispersed throughout the submucosa can be visualized. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE I.
Demographics.

Group	Number of patients	Age at CT scan (Mdn, IQR)	Years between IT surgery and CT (Mdn, IQR)	ENS6Q Score (Mdn, IQR)
ENS w/ SS	18	49, 36.3–55.3	14, 7.5–21.5	17.5, 15.3–21
ENS w/o SS	16	40, 33.8–56.5	8, 3.8–20	22, 19.8–23.8
p-values			$p = 0.195$	$p = 0.033$
Controls w/ hx of ITR	37	62, 54–67	14, 11–16	N/A*
Controls w/o hx of ITR	37	45, 38–56	N/A	N/A*

ENS = empty nose syndrome; ITR = inferior turbinate reduction.
*Assumed to be <11 given lack of ENS symptoms in clinical notes.

was additionally not significantly associated with the development of the Serpentine Sign (94% vs. 88%, respectively, $p > 0.05$).

The average septal mucosal thickness in our three cohorts (ENS with SS, ENS without SS, controls) was compared with CT imaging. While ENS patients had a greater median thickness (1.87, IQR = 1.27–2.44) than the control patients (1.44, IQR = 1.12–1.98), this did not reach statistical significance. In patients that met Serpentine Sign designation criteria, the difference between the thickness of the mucosal swellings and the mucosa between the swellings was significant ($p = 0.0002$).

Differences in the appearance of the septal mucosa in patients with and without the Serpentine Sign can also

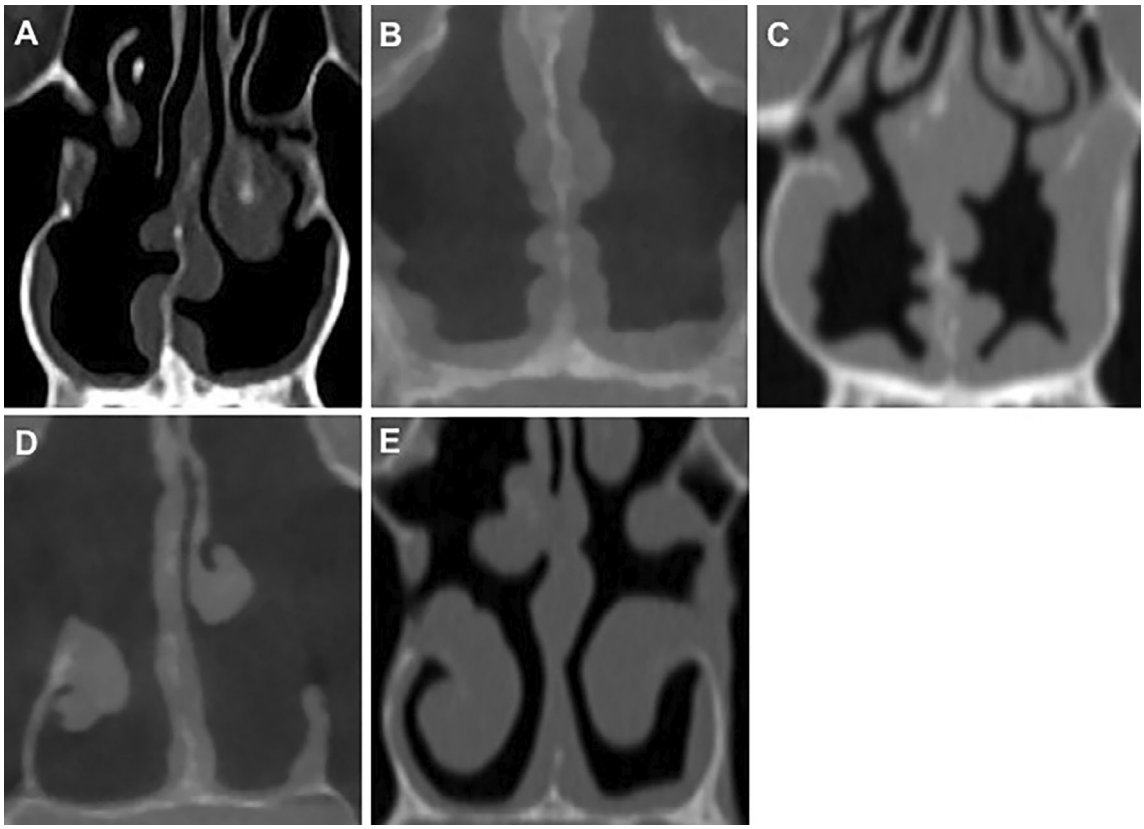

Fig. 3. Coronal computerized tomography (CT) imaging of Empty nose syndrome (ENS) and control patients. (A, B, C) ENS patients displaying the Serpentine Sign. (D) ENS patient without the Serpentine Sign. (E) Non-ENS, control patient without the Serpentine Sign.

be visualized during endoscopic examination (Fig. 4). On histologic analysis of this tissue, mucosal tissue that gave rise to the serpentine-like appearance revealed disorganized subepithelium rich in seromucinous glands. Figure 2 depicts septal mucosa from an ENS patient with the Serpentine Sign and a control patient with normal septal mucosa.

Sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) were calculated as follows: The specificity of the Serpentine Sign was 100%, the sensitivity 52.9%, the PPV 100%, and the NPV 80.1%. (Table II).

DISCUSSION

ENS is an uncommon yet often debilitating disorder that remains a diagnostic challenge. Patients suffer from a wide array of sinonasal symptoms, despite objectively patent airways.[21] Previous diagnostic criteria have been developed, such as the ENS6Q subjective test and the corresponding cotton test, both of which have proven to be essential in our practice.[2,15–18] Recently, newer tools have been developed, as seen in Dr. Zhao's group at The Ohio State University, which has shown consistent inferior and middle meatal airflow changes in ENS patients using computational fluid dynamics (CFD) of CT imaging.[2,22,23]

Just as CT imaging is essential in the diagnosis of other rhinological disorders such as chronic rhinosinusitis, CT imaging is also useful for ENS patients to evaluate the extent and location of turbinate tissue loss.[24] We have previously described altered radiographic findings in ENS patients, including a general increase in septal mucosal thickness.[19,20] In this study we describe a striking radiographic pattern that can be easily visualized on the coronal CT of patients with ENS given the undulating swelling nature of the nasal septum similar to the Rod of Asclepius (Fig. 5), which we term the Serpentine Sign, and investigate its use as a diagnostic tool for patients with ENS.

We noted that the association between the Serpentine Sign and ENS was significant ($p < 0.0001$) and postulate that the development of the Serpentine Sign occurs over time as the upper airway mucosa slowly compensates for significant airway tissue loss from past turbinate reduction. In fact, while not statistically significant, ENS patients who exhibited the Serpentine Sign had a greater median number of years between turbinate surgery and CT scans than ENS patients without the Serpentine Sign (14 vs. 8, $p = 0.195$). Continued monitoring of our ENS patient cohort without the Serpentine Sign may clarify if this feature is developed slowly over time as a compensatory mechanism.

ENS6Q scores were recorded to evaluate patients' ENS-related symptoms. We found that ENS patients without the Serpentine Sign had a significantly higher ENS6Q score (Median = 22, IQR = 19.25–25.25) compared to the ENS patients with the Serpentine Sign

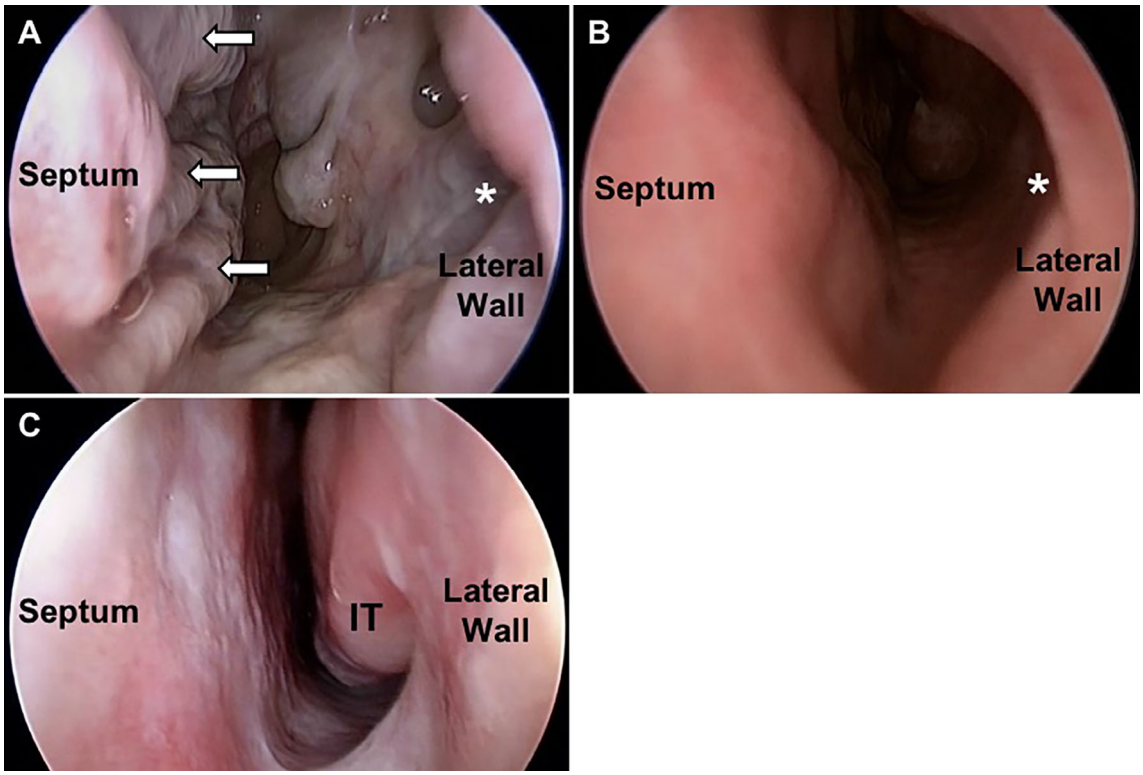

Fig. 4. Endoscopic imaging of Empty nose syndrome (ENS) and control patients. (A) Endoscopic image of the left inferior nasal cavity of an ENS patient with the Serpentine Sign demonstrating hypertrophy of septal mucosa (arrows) and inferior turbinate tissue loss (star). (B) Endoscopic image of the left inferior nasal cavity of ENS patient without the Serpentine Sign but with inferior turbinate tissue loss (star). (C) Endoscopic image of the left inferior nasal cavity of control patient without the Serpentine Sign, and with the left inferior turbinate (IT) intact. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Calculated Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of the Serpentine Sign.

		Cohort		
		ENS	Control	Total
Presence of SS (±)	+SS	18	0	18
	−SS	16	74	90
Total		34	74	108
Sensitivity			18/34 = 52.9%	
Specificity			67/67 = 100%	
PPV			18/18 = 100%	
NPV			74/90 = 82.2%	

ENS = empty nose syndrome.

(Median = 17.5, IQR = 14.75–21.75, $p = 0.033$). We hypothesize that these reduced scores in patients with the Serpentine Sign may be due to increased resistance in the nasal cavity from the additional "speedbumps" provided by the septal hypertrophy. This potentially increased airflow resistance could lead to decreased symptom severity and may explain the lower ENS6Q scores. Furthermore, we can reasonably conclude that there is an association between the Serpentine Sign with a positive ENS6Q in general, as a positive Serpentine Sign was found in 53% of the ENS cohort, versus 0% of the non-ENS cohort.

Fig. 5. The Rod of Asclepius. Created with BioRender.com. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Histologic analysis of the hypertrophied septum present in many of these ENS patients allows us to visualize and interpret the mucosal changes that may lead to this

distinctive finding. We noted a disorganized subepithelium and an increase in seromucinous glands, which resemble that of the nasal septal swell body as previously described by Dr. Wexler et al.[25] As described in that report, the nasal septal swell body shares structural similarities with an inferior turbinate and may play a role in the secretory function and vasoactive airflow regulation demonstrated by the presence of glandular tissue and expansile venous sinusoids.[25] In addition to the nasal airway resistance provided by the Serpentine Sign, we suspect that this hypertrophied mucosa may also have functional properties that could contribute to the reduction in symptoms experienced in the ENS group positive for the Serpentine Sign. Specifically, findings of increased glandular tissue found in the nasal septal swell body allow for adaptation to high velocity nasal airflow, and given the histological similarities between the nasal septal swell body and the tissue in the Serpentine Sign, may in part explain why patients with this finding have decreased symptom severity.[25] Future analysis with CFD may be useful in understanding specific airflow patterns in ENS patients who display the Serpentine Sign versus ENS patients who do not.

This type of compensatory mucosal hypertrophy has been proposed in other rhinologic conditions; a study by Kim et al. demonstrated that patients with septal deviations have compensatory hypertrophy of the inferior turbinate on the concave side of the deviation.[26] This hypertrophy was found to decrease after correcting the deviation through septoplasty.[26] Further analysis of this ENS-specific hypertrophic pattern using CT analysis alongside rhinometry and airflow measurements should be explored before and after inferior meatal augmentation procedures to understand whether this hypertrophy is potentially reversible following surgical intervention to reduce space in the nasal cavity.

We acknowledge that there are some limitations to this study. First, both our ENS and control cohorts include a relatively small number of patients. This is due to the rarity of ENS and our efforts to keep patients standardized. While we reviewed 470 control patients' charts, many did not have proper CT imaging, had diseases that might affect the integrity of the nasal mucosa, or met other exclusion criteria. Additionally, each patient had a variable amount of tissue loss following ITR, which makes standardization among patients challenging. In addition, some control patients had a history of maxillomandibular advancement surgery, which may affect the nasal cavity. Finally, since this was a retrospective study, control patients were unable to complete an ENS6Q to entirely rule out ENS resulting in clinical assumptions being made given the lack or presence of documented ENS within the clinical record.

Nonetheless, with a 100% PPV and specificity, radiographic or endoscopic visualization of the Serpentine Sign may be a useful radiographic marker in identifying ENS patients.

CONCLUSION

Here, we identify a clinically relevant radiographic finding deemed the "Serpentine Sign," which we find is unique to patients with ENS. This novel finding was not present in healthy control patients, regardless of turbinate surgical history, suggesting that this clinical and radiographic finding can be used as a reliable indicator of ENS. We hypothesize that this septal mucosal hypertrophy develops slowly over time, as a likely compensatory mechanism for turbinate tissue loss. The presence of this sign, in combination with patient symptoms, can serve as a useful diagnostic tool and aid for clinicians to consider when treating patients with a history of inferior turbinate reduction and concern for ENS.

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